Claims 53 and 65 have been deleted. Applicants reserve the right to pursue the subject matter of these originally filed claims in a continuing application.

New claims 99-112 have been added. Support for new claims 99-101 can be found in the specification on page 5, line 14. Support for new claims 102 and 103 can be found in the specification on page 8, lines 17-20. Support for new claims 104, 105 and 106 can be found in originally filed claim 55. Support for new claims 107 and 108 can be found in originally filed claim 57. Support for new claims 109 and 110 can be found in originally filed claim 66. Support for new claims 111 and 112 can be found in originally filed claim 67.

Claims 55, 57, 66, 67, 77-80, 82-85, 91, 94, and 97 have been amended. Claims 55, 66, 77, 82, and 85 have been amended, in part, in response to the Examiner's rejections under 35 U.S.C. 112, second paragraph.

Claim 55 has been re-written in independent form and includes the limitations of the claim from which it originally depended (i.e., claim 53). This amendment has been made in order to expedite prosecution of claims that read on a preferred commercial embodiment. A similar amendment was suggested by the Examiner and incorporated into claims of co-pending U.S. Patent Application No. 09/234,358, in order to expedite prosecution in that case. Additionally, the term "protein" has been added to clarify the original intent of the claim. Several members of the Markush group in claim 55 have been removed and placed into new claims 104, 105 and 106. All limitations of claim 55 which are currently pending were present in originally filed claim 55. Thus, this is not a narrowing amendment. Support for these amendments can be found in originally filed claims 53 and 55, and in the specification on page 3, lines 11-12 and page 9, lines 21-23.

Claims 57, 77, 78, 79, 80 and 82 have been amended to depend from claim 55 rather than now-deleted claim 53 or now-amended claim 77. Claims 67, 83, 84 and 85 have been amended to depend from claim 66 rather than now-deleted claim 65. The claim amendments are not related to patentability.

Claim 57 has been amended, in part, to clarify the original intent of the claim. A similar amendment was suggested by the Examiner and incorporated into claims of co-pending U.S. Patent Application No. 09/234,358, in order to expedite prosecution in that case. Two Markush group members within originally filed claim 57 have been removed and each is the basis of new claims 107 and 108. This is not a narrowing amendment.

Claim 66 has been re-written in independent form and includes the limitations of the claim from which it originally depended (i.e., claim 65). Additionally, the term "protein" has been added (for the same reasons discussed above) and the limitations of "multiple units carrying a polyaliphatic amine" and "at least 3 aliphatic amines spaced at discrete intervals along the polymer" have been removed for the sake of clarity. Several members of the Markush group in claim 66 have been removed and placed into new claims 109 and 110. All limitations of claim 66 which are currently pending were present in originally filed claim 66. Thus, this is not a narrowing amendment. Support for these amendments can

be found in originally filed claims 65 and 66, and in the specification on page 3, lines 11-12 and page 9, lines 21-23.

Claims 66, 67, 83, 84 and 85 have been amended to remove the phrase "of matter" in order to make the preamble consistent with other dependent claims. These claims are not narrowed as a result of these amendments. The claim amendments are not related to patentability.

Claim 67 has been amended to remove two Markush group members which are now the basis of new claims 111 and 112. The claim amendment is not related to patentability.

Claim 77 has been amended to narrow claim scope relative to the claim from which it now depends (i.e., claim 55). The scope of claim 77 is not affected by this amendment, and thus this is not a narrowing amendment. Support for this amendment can be found in originally filed claim 77.

Claims 79, 80, and 83 have been amended to recite proper antecedent basis with respect to the agent and the linking molecule. These claims are not narrowed as a result of these amendments. The claim amendments are not related to patentability.

Claims 82 and 85 have been amended to remove the redundant limitation of "in its native form free of conjugation to the linking molecule". This is not a narrowing amendment.

Claims 91, 94 and 97 have been amended to depend from claims which embrace preferred commercial embodiments. The claims amendments are not related to patentability. Support for these amendments can be found in originally filed claim 71, and in the specification on page 8, lines 17-20.

The specification has been amended to correct typographical errors. Support for these corrections can be found in the priority document U.S. Provisional Patent Application Serial No. 60/071,908 on page 1, first and second paragraphs, and page 19, second paragraph.

No new matter has been added.

**The Claimed Invention**

The claimed invention relates to compositions and kits for attaching active agents to body tissues using transglutaminase. The active agents are attached to body tissues via linking molecules. These linking molecules may be carboxamide-bearing substrates of transglutaminase, such as polymers with multiple glutamines. Alternatively, the linking molecules may be aliphatic amine-carrying substrates of transglutaminase, such as polymers with multiple lysines. Polymer units having a carboxamide or an aliphatic amine may be arranged in a contiguous or a non-contiguous manner along the length of the polymer.

The active agents are agents that, once coupled to a body tissue, have a desired activity such as a physiological or therapeutic activity. The agents are nonextracellular matrix proteins, nonlabeling agents including chemical agents such as pharmaceutical agents, sunscreen agents, ligands and/or receptors of

ligand-receptor pairs, insecticides, repellants, and microparticles. Importantly, the agents can be enzymes such as cholinesterase and phosphodiesterase, or they can be non-proteins.

The claimed kits optionally comprise another linking molecule in addition to the linking molecule of the conjugate. These second linking molecules can be used, for example, to prepare the body tissue by making the body tissue more receptive for interaction with the conjugate.

**Rejections under 35 U.S.C. 112, first paragraph**

Claims 86, 89, 92, 95 and 98 are rejected under 35 U.S.C. 112, first paragraph, because according to the Examiner, "the specification fails to enable a kit as claimed containing a third container containing a linking molecule that is a substrate of transglutaminase and that is covalently attached to the composition contained in the first container if in the presence of transglutaminase."

Applicants respectfully traverse this rejection. The specification provides support for these claims at least on page 7, lines 21-28, and page 16, lines 23-25. In particular the specification recites that "the kit can further comprise a third container housed by the package, the third container containing a linking molecule that is a substrate of transglutaminase and that is covalently bondable, in the presence of transglutaminase, to the composition in the first container." (See page 7, lines 23-26.) Further support can be found in originally filed claims 71 and 72, as well as in Figure 1 which illustrates a kit having three containers. The linking molecules of the first and third containers are distinct. An example of a linking molecule of the third container is a complementary linking molecule (see page 4, lines 9-19, and 27-31). The linking molecules of the third container can be used to prepare a body tissue for attachment of the conjugates of the invention (see page 16, lines 23-25). Accordingly, the specification provides sufficient support to enable a kit containing three containers as in claims 86, 89, 92, 95 and 98.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 86, 89, 92, 95 and 98 under 35 U.S.C. 112, first paragraph.

**Rejections under 35 U.S.C. 112, second paragraph**

Claims 53, 55, 57, 65-67, 71 and 74-98 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 53 is rejected because the phrase "linking molecule having a carboxamide, the linking molecule being a carboxamide-bearing substrate of transglutaminase" is confusing and unclear, according to the Examiner. Applicants have deleted claim 53 and re-written claim 55 in independent form to include all limitations of originally filed claim 53. In addition, claim 55 has been amended to clarify that the linking molecule is carboxamide-containing. Claim 55 as filed does not have the issue raised by the Examiner. It is believed that claim 55 was essentially allowable as filed and that it has not been narrowed in any way as a result of the re-write. Broader claims will be pursued in a continuing application.

Claim 55 is rejected because it depends from cancelled claim 54. Applicants have re-written claim 55 in independent form and removed the dependency to claim 54.

Claims 53 and 65 are rejected because they are confusing and unclear as to meaning and scope in their recitation of the terms "nonextracellular matrix" and "nonlabeling agent", according to the Examiner. Claims 53 and 65 have been deleted. Claims 55 and 66 have been re-written in independent form and they respectively embrace the limitations of originally filed claims 53 and 65. These claims have been amended to include the term "protein". The specification defines a non-extracellular matrix protein as being an agent that is not an extracellular matrix protein. (See page 3, lines 11-12; page 9, line 21-23.) Extracellular matrix proteins are located in the extracellular environment and contribute to the architecture between cells and within tissues. These proteins are known in the art and include but are not limited to fibronectin, collagen, thrombospondin, fibrillin, tenascin, laminin, osteospontin, and SPARC. Fibronectin is an example of an extracellular matrix protein that is a substrate of transglutaminase. The specification defines a non-labeling agent as one that is not simply a passive label with no function, when applied to a body tissue, other than being a label. (See page 9, lines 25-30.) The non-labeling agent has a function in addition to, or other than, merely being present and, as a result, being regarded solely as a passive label of cells or tissues. The term "non-labeling" means to exclude materials that are simply passive labels. Such materials are known to those of ordinary skill in the art. The specification also exemplifies such materials, specifically excluding labeled corneocyte proteins, labeled fibronectin, labeled extracellular matrix proteins, putrescine, dansylcadavearine, 5-(biotinamido)-pentylamine, and fluoresceincadaverine from the category of non-labeling agents. The elements of the Markush groups of claims 55 and 66 satisfy the definition of non-extracellular matrix protein and non-labeling agent.

Accordingly, a nonextracellular matrix, non-labeling agent is not a relative term nor is it subject to one's definition of an extracellular matrix protein or labeling, since the definitions of both are established in the art and further elaborated on in the specification. One of ordinary skill would understand, in light of the specification, that a nonextracellular, non-labeling agent is an agent which is not an extracellular protein and which possesses a function other than a passive labeling function.

Claim 65 is rejected because the phrase "polymer having multiple units carrying a polyaliphatic amine" is uncertain as to meaning and scope, according to the Examiner. Claim 65 is further rejected because the claim in unclear as to the relationship of the "at least 3 aliphatic amines" to the units and polyaliphatic amines, according to the Examiner. Claim 65 has been deleted. Claim 66 has been re-written in independent form and includes the limitations of claim 65 form which it originally depended. Claim 66 as filed does not have the issue raised by the Examiner. It is believed that claim 66 was essentially allowable as filed and that it has not been narrowed in any way as a result of the re-write. Broader claims will be pursued in a continuing application.

Claim 76 is rejected because the terms "polymer rich in glutamine" is uncertain as to meaning and scope, according to the Examiner. The specification defines a polymer rich in glutamine as a

molecule in which at least 20% of the units of the polymer are glutamine, or a molecule having at least three, preferably four and most preferably five contiguous, linked transglutaminase substrates (e.g., glutamines), preferably linked by peptide bonds. (See page 3, line 32, and page 4, lines 1-4.) Examples of polymers that are included in this definition are polymers that contain at least 30% glutamines, at least 40% glutamines, or 50% or more glutamines. (See page 4, lines 4-7.) Accordingly, an amount that is "rich" is neither relative nor subjective, based on the teaching provided by the specification.

Claim 77 is rejected because it is unclear as to how claim 53 is further limited, according to the Examiner. Applicants have amended claim 77 to depend from claim 55, and to read on a component of a high affinity noncovalent binding pair selected from the group consisting of a ligand of a ligand-receptor complex, and a receptor of a ligand-receptor complex.

Claim 82 is rejected because it is confusing to require that the agent, when in native form and free of conjugation to the linking molecule, not be a substrate for transglutaminase, according to the Examiner. In accordance with the Examiner's suggestion, claim 82 has been amended to remove the limitation "when in native form and free of conjugation to the linking molecule" because of the redundancy of this limitation. Claim 85 has been similarly amended.

Claims 86, 89, 92, 95 and 98 are rejected because their meaning and scope are uncertain as to a "third container containing a linking molecule that is a substrate of transglutaminase and that is covalently attached to the composition contained in the first container if in the presence of transglutaminase." The Examiner further contends that the specification does not describe a third container containing this linking molecule. As discussed above with respect to the rejection under 35 U.S.C. § 112, first paragraph, the specification does indeed provide support for kits containing three containers, and in particular, kits having a third container which contains a linking molecule. These claims intend that the linking molecule of the third container can be covalently attached to the conjugate of the first container. (See page 7, lines 23-26.)

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 53, 55, 57, 65-67, 71 and 74-98 under 35 U.S.C. 112, second paragraph.

**Rejections under 35 U.S.C. § 103(a)**

Claims 53, 55, 57, 65-67, 71 and 74-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richardson et al. (5,490,980), in view of Kahlem et al. (Reference CD), Greenberg et al. (Reference CF) and Davies et al. (Reference CA), and if necessary in further view of Green et al. (USP 5,525,336).

According to the Examiner, Richardson et al. disclose "a composition containing an active ingredient modified to contain an -RNH2 moiety where R is a straight aliphatic hydrocarbon chain of 1 to 8 carbon atoms and preferably at least 5 carbon atoms. Transglutaminase uses the -RNH2 moiety as a substrate to bind the active ingredient through the -RNH2 moiety to glutamine residues in skin, hair or nails. Most preferably the active ingredient contains more than one -RNH2 moiety in order to obtain

enhanced binding of the active ingredient." According to the Examiner, Kahlem et al., Greenberg et al., and Davies et al. "disclose transglutaminase crosslinking by acting on carboxamide-containing substrates" and Green et al. "disclose transglutaminase crosslinking proteins together by forming bonds between glutaminyl and lysyl residues."

The Examiner states that "it would have been obvious to link the active agent of Richardson et al. to a carboxamide-containing substrate of transglutaminase since it would have been expected from Kahlem et al., Greenberg et al., and Davies et al. that this substrate will substitute for the function of the -$RNH_2$-containing moiety of the active agent of Richardson et al. by the transglutaminase catalyzing a reaction between a carboxamide of peptide-bound glutamine and a primary amino group ($RNH_2$) of peptide-bound lysine." The Examiner further states that "to provide a polymer such as a lysine-containing protein or peptide having the -$RNH_2$ moiety for attaching the active ingredient of Richardson et al. would have been a matter of obvious choice since it would have been apparent from Kahlem et al., Greenberg et al., and Davies et al. that the carboxamide group and the primary amino group of $RNH_2$ can both be contained by a peptide or protein, and that crosslinking or attachment will occur irrespective of which protein or peptide contains the active ingredient." Finally, the Examiner states that the claimed kits would also have been obvious.

In order to render obvious the claimed invention, the combination of cited references must recite each and every element of the pending claims. In addition, a motivation must exist to combine the references in a manner that results in the presently claimed invention. Applicants respectfully traverse the rejection because these requirements have not been met.

The claimed invention has been described above.

Richardson et al. teach a method and composition for attaching an active agent to skin, hair or nails. The composition taught by Richardson et al. contains both transglutaminase and the active agent. Therefore, implicitly the active agent and transglutaminase must be simultaneously applied to skin, hair or nails in the method of Richardson et al. Richardson et al. teaches that transglutaminase is capable of forming crosslinks between proteins by inducing covalent bonds between glutamine and lysine residues. The reference further teaches that transglutaminase has a high specificity for protein-bound glutamine residues but a low specificity for lysine residues, and that a number of other amine-carrying compounds such as methyl amine, histamine and hydroxylamine are also suitable transglutaminase substrates.

The active agents used by Richardson et al. have, or are modified to have, an alkylamine group which reacts with glutamine residues in the skin, hair or nails of the subject. The general chemical formula for the modified active agent, shown in column 4, indicates that the active agent may have up to 4 alkylamine groups attached to it. However, each of 22 representative compounds taught by Richardson et al. contains only a single alkylamine group attached to the active agent. According to the formula taught by Richardson et al., none of the alkylamine groups corresponds to a lysine side chain given the placement of the amine group and its spacing along the aliphatic chain. Moreover, the alkylamine groups

are individually conjugated to the active agent and are not directly conjugated to each other. Suitable agents include anti-microbials, UV-absorbing materials, skin and hair conditioners, moisturizers, anti-inflammatory agents, anti-oxidants, coloring agents, and fragrances, and the reference provides the chemical structure of a number of examples for each class.

Richardson et al. do not teach a number of elements of the pending claims including (1) modification of active agents (and in particular non-protein active agents) by the addition of carboxamide groups such as glutamines (claims 53, 55, 57, 74, 75, 76); (2) modification of the active agent by addition of lysines (claim 66, 67); (3) modification of the active agent by addition of polymers rich in glutamine or lysine (claims 67, 76); (4) modification of the active agent by addition of carboxamide-carrying or aliphatic amine-carrying polymers. (claims 55, 57, 65, 66, 67, 74, 75); (5) modification of the active agent by addition of a polymer carrying at least 3 aliphatic amines spaced along the polymer (claim 65); (6) modification of the active agent by addition of contiguous carboxamides or aliphatic amines (claims 53, 55, 66, 74, 75); (7) active agents that are enzymes (claims 78, 100, 101); (8) use of endogenous transglutaminase (claims 53, 65); and (9) use of complementary linkers (claims 86, 89, 92, 95, 98).

The Greenberg et al. reference does not add to the teaching of Richardson et al. Greenberg et al. summarize common characteristics of transglutaminases, including their ability to catalyze a reaction between primary amines and the γ-carboxamide group of glutamine residues. The reference teaches bond formation between peptide bound lysine or polyamines and peptide bound glutamines. It further indicates that transglutaminases have a broad specificity for amines such as peptide-bound lysines or polyamines, yet possess a more restricted specificity for glutamines, as evidenced by the fact that few proteins contain glutamine residues suitable as transglutaminase substrates. (See page 3071, Enzymology.) In addition, the reference suggests that transglutaminase specificity for glutamines may be dependent upon the secondary structure and charge surrounding a glutamine residue. Greenberg et al. do not supply the deficiencies of Richardson et al. As an example, Greenberg et al. do not teach the carboxamide or aliphatic amine modification of active agents. Greenberg et al. also do not teach the modification of non-protein active agents. Instead, the reference teaches away from both of these elements.

The Davies et al. reference also does not add to the teaching of the Richardson et al. Davies et al. teach the ability of transglutaminases to crosslink proteins by inducing bond formation between protein-bound glutamines and protein-bound lysines or polyamines. The reference re-iterates the teaching of Greenberg et al. that transglutaminases are highly selective of glutamine residues that can act as substrates. For example, it states that transglutaminases react specifically with glutamine residues that are protein bound. Yet the reference teaches that few protein bound glutamine residues are suitable substrates for transglutaminase, and that reactivity is likely determined by secondary structure and amino acid sequence in the vicinity of the glutamine residue. In proteins that are substrates of transglutaminase, only a single glutamine residue is apparently involved. In contrast to their strict specificity for glutamines, transglutaminases have a more relaxed requirement for amines, and can react with protein bound amines

and free polyamines equally well. The relaxed transglutaminase specificity for amines can be exploited in order to produce a wide variety of diverse reaction products. Accordingly, Davies et al. also fail to supply the deficiencies of Richardson et al. Davies et al. do not teach carboxamide modification of active agents, particularly non-protein active agents and, like Greenberg et al., teach away from these claimed elements. Davies et al. also fail to disclose modification of active agents with contiguous carboxamides, or contiguous or non-contiguous aliphatic amines.

The Green et al. reference similarly does not add to the teaching of Richardson et al. Green et al. teach the attachment of naturally occurring proteins, namely corneocyte proteins, to skin, hair or nails, as cosmetic formulations. The reference teaches that corneocyte proteins can be attached to these surfaces using a crosslinking agent such as transglutaminase. Green et al. do not supply the deficiencies of Richardson et al. The reference does not teach modification of active agents with either lysine or glutamine addition.

The Kahlem et al. reference studies the involvement of polyglutamine containing peptides and polypeptides in the progression of neurodegenerative diseases. Like the other secondary references cited by the Examiner, Kahlem et al. teach that in order for a glutamine residue to be a substrate of transglutaminase, it must be present in the context of a peptide or a protein. The reference indicates that polyglutamines ranging in length from 2 to 18 residues can act as amine acceptors in a transglutaminase catalyzed reaction. Kahlem et al. do not suggest that polyglutamines have utility in drug delivery formulations. This is significant since two of the authors of the Kahlem et al. reference are co-inventors of the present invention. Clearly, these co-authors did not recognize that polyglutamines could be applied to the delivery of active agents to subjects. Rather, they were focused on the impact of naturally occurring polyglutamines in the body, and their role in the progression of certain neurodegenerative diseases. For this reason, persons of ordinary skill in the art would not look to the Kahlem et al. reference for guidance on how to modify the teachings of Richardson et al.

The prior art as a whole teaches that transglutaminase has a restricted specificity for glutamines. To be suitable transglutaminase substrates, glutamines must be provided in the context of a peptide or a protein, according to the prior art. In addition, the prior art repeatedly teaches that transglutaminase exhibits a relaxed specificity for amines. These teachings imply that the choice of glutamine-bearing substrates of transglutaminase is limited as compared to the choice of amine-bearing substrates of transglutaminase. This leads to the conclusion that amine-carrying substrates, and not glutamine-carrying substrates, impart the variation and diversity found in transglutaminase reaction products. In view of these prior art teachings, one of ordinary skill in the art would not choose to modify active agents with carboxamide groups, particularly when those active agents are not protein in nature. Only the present invention teaches the use of carboxamide-modified active agents as transglutaminase substrates.

By combining the Richardson et al. reference with Kahlem et al., the Examiner is engaging in impermissible hindsight. In the absence of the present invention, there is nothing in either reference to

motivate one of ordinary skill in the art of drug delivery to look to the Kahlem et al. reference as providing a teaching relevant to the field of drug delivery, since the Kahlem et al. reference is primarily directed at studying the mechanisms of certain neurodegenerative diseases while Richardson et al. is directed at agent delivery for cosmetic and therapeutic purposes.

For these reasons, the combinations of references suggested by the Examiner either do not render the claimed invention obvious or are at least impermissible.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdrawn the rejection under 35 U.S.C. §103(a).

**Summary**

Applicants believe that each of the pending claims now is in condition for allowance. Applicants respectfully request that the Examiner telephone Applicants' attorney in the event that the claims are not found to be in condition for allowance.

If the Examiner has any questions and believes that a telephone conference with Applicants' attorney would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 720-3500 (extension 232).

Respectfully submitted,

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Attorney's Docket No.: H0535/7009 (ERG/MAT)
Date: March 5, 2001
**x03/05/01**

**MARKED-UP CLAIMS**

55. (Amended) [The composition of claim 54,] A composition of matter comprising:

a conjugate of a nonextracellular matrix protein, nonlabeling agent and a carboxamide-carrying linking molecule,

wherein the agent is selected from the group consisting of a sunscreen agent, a cosmetic, an enzyme, a coloring agent, a pharmaceutical agent, a member of a ligand/receptor pair, a tissue sealant, a bulking agent, a hair conditioning agent, a hair fixative, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellant and a component of a high affinity noncovalent coupling pair;

wherein the linking molecule is not native to the agent, and

wherein the linking molecule comprises [is selected from the group consisting of:

(a) at least one glutamine,

(b)] at least two contiguous linked glutamines, and is a substrate of transglutaminase.

[(c) at least three linked glutamines,

(d) at least four linked glutamines, and

(e) at least five linked glutamines.]

57. (Amended) The composition of claim [53] 55, wherein the linking molecule comprises a polymer of amino acids [and wherein the amino acids are selected from the group consisting of] containing[:] at least 20% [of the amino acids are] glutamines[, at least 30% of the amino acids are glutamines, and at least 40% of the amino acids are glutamines].

66. (Amended) [The composition of matter of claim 65,] A composition of matter comprising:

a conjugate of a nonextracellular matrix protein, nonlabeling agent and a polymer,

wherein the agent is selected from the group consisting of a sunscreen agent, a cosmetic, an enzyme, a bulking agent, a hair conditioning agent, a hair fixative, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, a coloring agent, a pharmaceutical agent, a member of a ligand/receptor pair, a tissue sealant, an insect repellant and a component of a high affinity noncovalent coupling pair, and

wherein the polymer comprises at least 3[, at least 4 or at least 5] contiguous lysines attached to one another by peptide bonds, and is a substrate of transglutaminase.

67. (Amended) The composition [of matter] of claim [65] 66, wherein the polymer comprises amino acids, and wherein at least 20%[, at least 30% or at least 40%] of the amino acids are lysines.

77. (Amended) The composition of claim [53] 55, wherein the component of a high affinity noncovalent binding pair [agent] is selected from the group consisting of [a sunscreen agent, a cosmetic agent, a bulking agent, a hair conditioning agent, a hair fixative, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellant an enzyme, a coloring agent, a pharmaceutical agent,] a ligand of a ligand-receptor complex, and a receptor of a ligand-receptor complex[, and a component of a high affinity noncovalent binding pair].

78. (Amended) The composition of claim [77] 55, wherein the agent is selected from the group consisting of a cholinesterase and a phosphodiesterase.

79. (Amended) The composition of claim [53] 55, wherein [the bond between] the agent is conjugated to [and] the linking molecule by a bond that is hydrolyzable under physiological conditions.

80. (Amended) The composition of claim [77] 55, wherein the agent is a pharmaceutical agent and [the bond between] the agent is conjugated to [and] the linking molecule by a bond that is hydrolyzable under physiological conditions.

82. (Amended)) The composition of claim [53] 55, wherein the agent [in its native form free of conjugation to the linking molecule] is not itself a substrate of transglutaminase.

83. (Amended) The [compositions of matter] composition of claim [65] 66, wherein [the bond between] the agent is conjugated to [and] the linking molecule by a bond that is hydrolyzable under physiological conditions.

84. (Amended) The composition [of matter] of claim [65] 66, wherein the agent is a nonprotein.

85. (Amended) The composition [of matter] of claim [65] 66, wherein the agent [in its native form, free of conjugation to the linking molecule,] is not itself a substrate of transglutaminase.

91. (Amended) A kit comprising

a package housing:

a first container containing the composition of claim [77] 81, and

a second container containing transglutaminase.

94. (Amended) A kit comprising

a package housing:

a first container containing the composition of claim [67] 84, and a second container containing transglutaminase.

97. (Amended) A kit comprising

a package housing:

a first container containing the composition of claim [85] 102, and a second container containing transglutaminase.

**MARKED-UP SPECIFICATION**

Please re-write the two paragraphs beginning on page 1, line 16 as follows:

Transglutaminases are a family of calcium-dependent enzymes mediating covalent cross-linking reactions between specific peptide bound [(-glutamyl] γ-glutamyl residues and various primary amino groups of peptide-bound lysines or polyamines, acting as amine donor substrates (Davies, et al., *Adv. Exp. Med. Biol.* 250, 391-401, 1988). These enzymes stabilize biological structures via the formation of isopeptide cross-links. In mammals, at least five enzymatically active transglutaminases have been identified, cloned and sequenced. The number of proteins acting as glutaminyl substrates for transglutaminases is restricted, and no obvious consensus sequence around these substrates' glutamines has been found.

Three main lines of investigation have been conducted surrounding transglutaminases. These enzymes have been used to label membrane proteins and, in the absence of exogenous amines, to catalyze the formation of [((-glutamine)]-lysyl] (γ-glutamyl)-lysyl cross-links between them. The labeling is quite specific and can be carried out under mild (physiological) reaction conditions. Thus, for example, transglutaminases were used to study rhodopsin in the intact disc membrane, as only residues of rhodopsin located in the aqueous phase in the exposed side of the disc membranes were expected to be labeled. In these experiments, rhodopsin was labeled by transglutaminase using putrescine and dansylcadaverine as detectable substrates.

Please re-write the paragraph beginning on page 2, line 28 as follows:

It has been discovered, surprisingly, that certain substrates of transglutaminase are particularly desirable for use as linking molecules to attach agents to proteinaceous material such as body tissue. It also has been discovered that molecules, including native peptides and conjugates according to the invention, can be screened to determine those that can be substrates of transglutaminases, and then such molecules can be attached to body tissue. [Method] Methods of attaching agents to body tissue and methods of screening molecules using transglutaminase are provided. In addition, compositions of matter suitable as substrates for transglutaminase and kits containing such molecules together with transglutaminase are provided.

Please re-write the paragraph beginning on page 9, line 4 as follows:

The invention is based in part on the discovery that polymers bearing multiple reactive (with transglutaminase) carboxamides or multiple reactive aliphatic amines are particularly useful linking molecules for attaching agents to [protienaceous] proteinaceous material such as skin and hair. The

closest prior art teaches away from using carboxamides and also from using polymers bearing multiple reactive aliphatic amines as defined herein, for such a purpose as described in greater detail below.

Please re-write the paragraph beginning on page 10, line 28 as follows:

Preferred linking molecules are polymers bearing multiple reactive carboxamides and/or aliphatic amines that are substrates of transglutaminase. Carboxamides that are substrates of transglutaminase are well known and include [glutaminase] glutamines. Aliphatic amines that are substrates of transglutaminase also are well known and are exemplified in, for example, U.S. patent 5,490,980, the disclosure of which is incorporated herein by reference. Unlike the '980 patent, however, which depicts single aliphatic amine moieties and plural such moieties as independent substituents in certain circumstances, the present invention involves in one aspect using a plurality of aliphatic amines spaced apart at discrete intervals, preferably along the length of a branched or unbranched polymer. It has been discovered, surprisingly, that the spacing of the reactive moieties can be important to achieving the results of the present invention.